Table 7-16. PUFs and BAFs for WAG 4 nonradionuclide contaminants (unitless).

	PUF[a,b]	BAF[a,c] for Insectivores	BAF[a,c] for Predators	BAF[a] for Omnivores
Inorganic Contaminants				
Antimony	2.0E-02	9.0E-01	6.0E-03	9.0E-01
Arsenic	4.0E-02	1.0E+00	4.0E-02	1.0E+00
Barium	1.5E-02	1.0E+00	1.5E-02	1.0E+00
Cadmium	5.5E-01	1.1E+00	1.9E+00	1.9E+00
Chromium III	7.5E-03	6.0E-02	2.0E-01	2.0E-01
Cobalt	1.1E+00	1.1E+00	2.0E-02	1.0E+00
Copper	4.0E-01	1.0E+00	2.0E-01	1.0E+00
Lead	4.5E-02	3.0E-01	6.0E-01	6.0E-01
Manganese	9.8E+00	1.0E+00	2.5E-01	1.0E+00
Mercury	9.0E-01	4.0E-01	7.0E-01	7.0E-01
Nickel	6.0E-02	1.0E+00	6.0E-03	1.0E+00
Nitrate	1.0E+00	1.0E+00	1.0E+00	1.0E+00
Selenium	2.5E-02	1.0E+00	2.5E-02	1.0E+00
Silver	4.0E-01	1.0E+00	4.0E-01	1.0E+00
Vanadium	5.5E-03	1.0E+00	1.0E+00	2.5E-03
Zinc	1.5E+00	1.0E+00	7.0E-01	1.0E+00
Organic Compounds[d]				
Acetone	5.3E+01	5.5E-07	5.5E-07	5.5E-07
Aroclor-1254	1.3E-02	4.0E-04	4.0E-04	4.0E-04
Benzo(a)anthracene	2.3E-02	1.0E-02	1.0E-02	1.0E-02
Benzo(a)pyrene	1.2E-02	4.1E-04	4.1E-04	4.1E-04
Benzo(b)fluoranthene	1.2E-02	4.1E-04	4.1E-04	4.1E-04
Benzo(g,h,i)perylene	6.7E-03	6.5E-04	6.5E-04	6.5E-04
Benzo(k)fluoranthene	1.2E-02	4.1E-04	4.1E-04	4.1E-04
Chrysene	2.2E-02	2.5E-04	2.5E-04	2.5E-04
Dibenz(a,h)anthracene	1.2E-02	4.1E-04	4.1E-04	4.1E-01
Indeno(1,2,3-cd)pyrene	6.8E-03	6.5E-04	6.5E-04	6.5E-04
Pyrene	5.8E-02	1.9E-03	1.9E-03	1.9E-03
TPH	1.0E+00	1.0E+00	1.0E+00	1.0E+00
Xylene	5.0E-01	2.2E-05	2.2E-05	2.2E-05

a. Development and/or calculation of PUFs and BAFs are documented in Appendix J.

b. PUF = Plant uptake factor.

c. BAF = Bioaccumulation factor.

d. The following organic compounds were not assessed: 2-methylnaphthalene, 4-methyl-2-pentanone, benzo(a)anthracene, pyrene, chloromethane, dibenzofuran and pentachlorophenol.

The PUF for organics is estimated using the geometric mean regression equation developed by Travis and Arms (1988) and using log K_{ow} values. The reliability of estimated PUFs is directly related to the reliability of the K_{ow} values used for the organic compounds. Since K_{ow} values can vary greatly, use of the Travis and Arms (1988) equation to estimate a PUF for organic compounds may over- or underestimate the true dose for organic compounds.

There is a great deal of uncertainty associated with the bioaccumulation factors (BAFs) used to calculate dose. Very few BAFs are available in the scientific literature, since they must be both contaminant- and receptor-specific. In the absence of specific BAFs, a value of 1 was assumed. This assumption could over- or underestimate the true dose from the contaminant, and the magnitude of error cannot be quantified. Travis and Arms (1988) and Baes et al. (1984) report BAFs for contaminants to beef and milk; all of these are less than 1 for the contaminants at WAG 4. If the terrestrial receptors of concern accumulate metals and PCBs in a similar way and to a comparable degree as beef and dairy cattle, the use of a BAF of 1 for all contaminants and receptors would overestimate the dose. On the other hand, if the terrestrial receptors of concern for WAG 4 accumulate metals and PCBs to a much larger degree than beef and dairy cattle, the assumption of BAFs equal to 1 could underestimate the true dose from the COPCs.

7.3.2.6 Uncertainty Associated with Soil Ingestion. The exposure assessment incorporates percentage of soil ingested by each representative of the functional groups. Although food ingestion rates have the greatest effect on intake estimates, soil ingestion rates could also influence intake rates and, therefore, dose estimates. The EPA Wildlife Exposure Factors Handbook (EPA 1993a), Beyer et al. (1994) and Arthur and Gates (1988) were used to assign soil ingestion parameters for functional groups and individual species. Estimating the percent soil ingested may over- or underestimate the dose since the effect of the estimated values on the overall dose outcome is dependent on the concentration of contaminant in the media of concern.

7.3.3 Ecological Effects Assessment

Ecological effects assessment consists of three elements:

- Selecting quantified critical exposures (QCEs)
- Developing AFs
- Developing TRVs.

Sections 7.3.3.1 through 7.3.3.4 below contain a general description of the procedures of ecological effects assessment and discussions of each of the three elements.

7.3.3.1 General Procedures. A TRV is defined as a dose for a receptor (including sensitive subgroups such as taxa under regulatory protection) that is likely to be without appreciable risk of deleterious effects from chronic exposure. Application of toxicity data derived from surrogate species introduces uncertainty into the risk assessment. The magnitude of this uncertainty depends largely upon (1) the degree of taxonomic difference between the key and test species, (2) the conditions under which the toxicity data are obtained, and (3) the endpoint of interest [e.g., chronic lowest-observed-adverse-effect-level (LOAEL) or no-observed-adverse-effect-level (NOAEL)] and the endpoint measured (e.g., death). Uncertainties associated with extrapolation of toxicity information from literature to site conditions can therefore be offset by applying AFs to the endpoint values identified in the literature.

The approach for TRV derivation used in this WAG ERA was developed by Ludwig et al. (1993) for use at the Rocky Mountain Arsenal Superfund site in Commerce City, CO, and is generally based on the EPA reference dose approach as modified by Lewis et al. (1990). It is predicated on the development and application of AFs, which are intended to explicitly account for variations and uncertainties in the data and necessary extrapolations from it. The types of variation and extrapolation uncertainties explicitly quantified are:

- Variation in sensitivity among the members of a receptor population
- Uncertainty in extrapolating data from one taxon to another
- Uncertainty in using various effect levels to estimate no-effect levels in receptors
- The inability of any single study to adequately address all possible adverse outcomes in a wild receptor population.

The approach of Ludwig et al. (1993) offers several distinct advantages. By carefully identifying the specific types of adjustments needed in the extrapolation, this method permits maximum resolution of what each adjustment is intended to achieve. It emphasizes consensual, data-quality-based development of values for specific AFs rather than defaulting to arbitrary factors. It clearly discriminates between "best estimates" of the values of individual factors and adjustment for overall uncertainty, including the uncertainty associated with the AFs themselves.

The TRVs used for antimony, arsenic, barium, cadmium, chromium, cobalt, copper, lead, manganese, mercury, nickel, selenium, silver, thallium, toluene and zinc for plants were taken directly from Suter et al. (1993) and no AF values were assigned. The values presented in that paper are toxicological benchmarks for screening potential COCs for effects on terrestrial plants in soil. These values are for those contaminants potentially associated with DOE sites and were, therefore, appropriately used in the calculations for the INEEL.

7.3.3.2 Selecting Quantified Critical Exposures. TRV development is initiated by reviewing the available toxicological literature and relevant databases for each contaminant and functional group members to identify quantified critical exposures (QCEs) from the best available study. Studies considering nonlethal endpoints and reporting NOAELs are selected, if available. Those reflecting reproductive competence are most preferred as such endpoints are considered to best reflect the population-level impacts of greatest concern in ERA. The following criteria are used to select QCEs:

- Experimental taxa should be as similar as possible to receptors at INEEL site(s), both physiologically and ecologically. With respect to body size, feeding, and behavioral habits, anatomy, and physiology, the surrogate species should be matched as closely as possible to the receptors.
- Test exposure route and medium should be similar to that expected for receptors in the field. For most of the receptors at INEEL, exposure media are limited to soil and dietary items (both animal and vegetable). Liquid intake is largely in the form of metabolic water. Dietary laboratory studies are therefore the most appropriate models for extrapolation. Gavage and drinking water studies will be considered, if necessary, but reduce confidence in the applicability of the study.

- Long-term (preferably lifetime) exposures should be used, as they are closest to exposure patterns occurring in the field.

- Experimental endpoints should represent ecologically significant effects at the population level. In general, loss of a few individuals of a species is unlikely to significantly diminish the viability of the population or disrupt the community or ecosystem of which it is a part. As a result, the fundamental unit for ERA is generally the population rather than the individual, with the exception of T/E and sensitive species (EPA 1992). In general, the most appropriate endpoints for ERA are reproduction, neurological function, and growth and development. For species under regulatory protection, TRVs are based on the most sensitive nonlethal endpoints referring specifically to individuals.

- Doses within the NOAEL-LOAEL bracket should be identified. If these data are not available, the following dose levels (in decreasing order of preference) may be used: chronic-nonlethal-adverse-effect-level > no-effect-level > frank-effect-level (including lethality). The definition of adversity requires considerable analysis of the potential ecological significance of the effects reported. For example, elevated liver weight or enzyme induction could represent an adaptive response rather than a toxic injury.

- Studies should be of high quality, defined as complete in design, with adequate numbers of subjects and dose levels, lifetime duration, explicit analysis of experimental uncertainty, clear results, and well-justified conclusions.

If a single study cannot be selected (e.g., where only acute exposure, lethal endpoint studies are available), then an average of several studies of similar quality using the same or closely similar species may be used. In averaging, extreme outliers, which are defined as greater than two standard deviations from the mean, are excluded. Where similar endpoints are observed in more than one study of similar quality, the lowest QCE should be used.

Information on the toxicological effects on mammalian receptors of the following contaminants is not available. Therefore, these contaminants were not evaluated for potential risk for mammalian receptors.

- 4-methyl-2-pentanone
- chloromethane
- dibenzofuran
- pentachlorophenol

Information on the toxicological effects to avian receptors of the following contaminants was not located. Therefore, these contaminants could not be evaluated for potential risk to avian receptors.

- 4-methyl-2-pentanone
- acetone
- antimony
- barium
- benzo(a)anthracene
- benzo(a)pyrene
- benzo(b)fluoranthene
- benzo(g,h,i)perylene
- benzo(k)fluoranthene
- chloromethane
- chrysene
- dibenz(a,h)anthracene

- dibenzofuran
- indeno(1,2,3-cd) pyrene
- pentachlorophenol
- pyrene
- xylene

7.3.3.3 Developing AFs. Six AFs for extrapolation from experimental studies to field exposures at the INEEL are defined for

I = intrataxon variability

R = intertaxon variability

Q_1 = risk assessor's certainty that the COPC actually causes the critical effect in the receptor, and that it is an ecologically significant effect

Q_2 = extrapolation from short- to long-term EDs

Q_3 = extrapolation across endpoint types to estimate an NOAEL

U = any residual uncertainty in the data evaluation process and estimation of other AFs based on data quality, study design, and known but otherwise unaccounted for extrapolation issues

M = professional judgement to determine another uncertainty factor (M) that is < 10. The magnitude of the M depends upon the professional assessment of scientific uncertainties of the study and database not explicitly treated above; e.g., the completeness of the overall database of the number of animals tested. The default value of M is 1.

Values for these AFs are set based on the quality of the selected study in particular, and of the database in general. Other potentially influential factors include the ecological circumstances of the receptor, regulatory criteria and standards, background contaminants levels, and protection status. To prevent needless overestimation of risk, the maximal AF product (all AFs multiplied together) is scaled to the overall extrapolation error observed in experimental studies designed specifically to determine the uncertainty in such extrapolations. Barnthouse et al. (1990) quantified the range of maximal uncertainty necessary to permit extrapolation of various kinds of toxicity data for various taxa of finfish at the population level. The types of toxicity data used included studies involving particular species of interest and other species, for acute, partial life-cycle, and full life-cycle exposures. The range of maximal uncertainty varied with the type of data used, and ranged from approximately 200 to 400 (Barnthouse et al. 1990). It is assumed that the degree of variability observed among fish taxa is similar to that occurring among other vertebrate taxa.

Based on a systematic review of all available information (Ludwig et al. 1993), a simple, relative scale is developed consisting of "low," "medium," and "high" rankings for each AF, with adjustments made of the basis of specific inherent uncertainty or variability in the particular extrapolations. The quantitative valuation of this scale is designed to be constrained by an upper bound in the range of 200 to 400, and use the most plausible values for each AF.

Specific values for these AFs and a brief description of criteria for their use are presented in Table 7-17. Values for all AFs except Q_1 and M are set at 1 ("low"), 2 ("medium"), and 3 ("high"), with

Table 7-17. AF values and criteria used to develop TRVs for the INEEL.

Adjustment Factor	Qualitative Ranking	Value	Criteria
I	Low	1	Variability is low
	Medium	2	Variability is moderate or average
	High	3	Variability is high, or information on variability is inadequate
R	Low	1	Test organism and functional group, T/E, C2 are in same taxonomic order and trophic category
	Medium	2	Test organism and functional group, T/E, C2 are in same trophic category but different taxa
	High	3	Test organism and functional group, T/E, C2 are in different trophic categories
Q_1	Low	0.1	Experimental endpoint is highly unlikely to occur in the field
	Medium	0.5	Experimental endpoint is moderately unlikely to occur in the field
	High	1	Experimental endpoint is likely to occur in the field
Q_2	Low	1	Study was of chronic duration
	Medium	2	Study was of subchronic duration
	High	3	Study was of acute duration
Q_3	Low	1	NOAEL
	Medium	2	LOAEL
	High	3	Adverse effect level or frank effect level
U	Low	1	High quality studies
	Medium	2	Studies of reasonable quality
	High	3	Studies with flawed design or incomplete information
M	—	<10	Use professional judgement to determine another uncertainty factor (M).

lower values generally representing greater confidence that the QCEs correspond well with "safe" doses for receptors. The factor Q_1, which expresses the degree of certainty that the experimental effect will not occur in the field or is not of ecological significance, runs on a positive scale equivalent where 0.1 represents high certainty that the effect either does not occur in the receptor or is ecologically irrelevant; 0.5 represents moderate certainty that the effect does not occur or is irrelevant; and, 1 represents reasonable certainty that the effect will occur in the receptor species and is ecologically significant. The factor M is used to adjust uncertainty based on professional judgement. For example, M can be set at 1 if the medium of exposure in the QCE study is similar to field exposure media at this site (i.e., primarily food and soil ingestion). However, because a number of toxicological studies for metals used soluble salts in drinking water as a means of exposure and both the contaminant species and exposure matrix tend to maximize metal absorption (Steele et al. 1990; Griffin and Turuk 1991; Witmer et al. 1991), M may be set at 0.5 to conservatively represent the significantly lower bioavailability of the metal species associated with soils and dietary items in the natural environment. Without M being greater than 1.0, the maximum product of the seven AFs is 243. This AF maximum represents the extent to which valid extrapolation of the data can be applied across experimental protocols or among taxa. More detailed information on the definition and valuation of these factors is available in Ludwig et al. (1993).

7.3.3.4 Developing TRVs. The third element in ecological effects assessment is the derivation of TRVs. TRVs were derived for each functional group by selecting the experimental study with the most appropriate QCE for that chemical and assigning numerical values for all AFs to account for uncertainties associated with extrapolation across species and exposure conditions. The algorithm used for deriving a TRV is

$$TRV = \frac{QCE}{AF} \tag{7-32}$$

where

QCE = quantified critical exposure

AF = $[I] \times [R] \times [Q_1] \times [Q_2] \times [Q_3] \times [U] \times [M]$.

Information used to derive TRVs for nonradioactive inorganic and organic contaminants is summarized in this section. The development of TRVs for each contaminant/functional group combination is presented in Appendix J for mammalian and avian receptors. Table J-1 summarizes the TRVs for mammalian functional groups. A summary of the TRVs for avian functional groups is contained in Table J-2. Shading in Tables J-1 and J-2 corresponds to the TRVs chosen for each functional group. When the test organism and the receptor were in the same taxonomic order and trophic category (R = 1), the corresponding TRV was chosen, as shown in heavier shading. If the test organism and receptor are in the same trophic level and different taxa, R = 2 was used. Otherwise, the minimum TRV (R = 3) for each COPC was chosen for all mammalian or avian receptors. Little information was found describing the effects of COPCs on reptilian, invertebrate, or terrestrial plant receptors. When available, that information is summarized in Sections 7.3.4 and 7.3.5. Development of TRVs for radionuclides is described in Section 7.3.6.

7.3.4 Development of TRVs for Inorganic Contaminants of Potential Concern

This section contains summaries on the information used in determining the TRVs for the inorganic contaminants for which toxicological studies were located. This information and the adjustment factors used are presented in Appendix I. The inorganic contaminants include:

- antimony
- arsenic
- barium
- cadmium
- chromium
- cobalt
- copper
- lead
- manganese
- mercury
- nickel
- nitrate
- selenium
- silver
- sulfate
- thallium
- vanadium
- zinc

Antimony (CAS No. 7440-36-0). Antimony causes a number of toxic effects in animals, including suppression of weight gain, shortened life span, and damage to liver, heart, thyroid, and kidneys. Trivalent compounds (e.g., antimony trioxide, antimony trisulfide) are about 10 times more toxic than pentavalent forms. The gastrointestinal absorption of trivalent antimony is about 15 - 36% (Weitz and Ober 1965; van Bruwaene et al. 1982; Gerber et al. 1982). The acute toxicity of antimony trioxide is low, with an oral LD_{50} in rats of greater than 20 g/kg (Smyth and Carpenter 1948).

In chronic studies, 5 mg/L potassium antimony tartrate (approximately 0.35 mg/kg-day) in drinking water is associated with slightly decreased life spans in rats (Schroeder et al. 1970) and female mice (Schroeder et al. 1968; Kanisawa and Schroeder 1969). Endpoints examined in these chronic (lifetime) studies included growth and body weight, median life span, longevity, tumor incidence, and histopathology. Other ecologically relevant endpoints (e.g., reproduction) were not examined, and only one dose was administered. Although rats appeared to be more sensitive than mice in these studies, the effects reported are of questionable ecological significance.

No information on the toxicological effects of antimony on avian receptors was located.

Arsenic (CAS No. 7440-38-2). Arsenic is a metalloid element that is widespread in all environmental media, making up about 0.0005% of the earth's crust. Arsenic is commonly present in living organisms and is constantly being oxidized, reduced, or metabolized.

The potential toxicity of arsenic to any organism is dependent on its chemical form. Inorganic arsenicals are generally more toxic than organic arsenicals, and trivalent forms are more toxic than pentavalent forms. Toxicity is related to aqueous solubility, and the order of toxicity (from greatest to least) is arsines > inorganic arsenites > organic trivalent compounds > inorganic arsenates > organic pentavalent compounds > arsonium compounds > elemental arsenic (Eisler 1988a).

Chemical properties contributing to arsenic's toxicity include its ability to bind to protein sulfhydryl groups and to substitute for phosphorus in some biochemical reactions. These chemical properties may also be responsible for arsenic's apparent essentially in several mammalian species (e.g., Frost 1983; Uthus 1992). In fact, arsenical feed additives are used to promote growth in a number

of agricultural species (Eisler 1988a). Recent studies have suggested that arsenic has a physiological role in the formation of various metabolites of methionine metabolism (Uthus 1992). The arsenic requirement for growing chicks and rats is approximately 25 mg/kg diet (Uthus 1992). Species differences in the pharmacokinetic disposition of arsenic have significant effects on their sensitivity to its toxic effects. In addition, animals exposed to sublethal levels of arsenic can develop tolerance to subsequent exposures (Eisler 1988a).

A subacute study using domestic sheep was documented (Eisler 1988a) in which a NOEL endpoint using 2.3 mg/kg-day was reported. An LOAEL of 1.5 mg/kg-day was reported in a chronic study using sodium arsenate in rats (Byron et al. 1967). The data did not show a good dose-response curve in the low-dose range.

The National Academy of Sciences reported an LD_{50} of 39 mg/kg-day using sodium arsenite in mallards.

Barium (CAS No. 513-77-9). Little information regarding the toxicity of barium is available. Its acute toxicity is low, with LD_{50}s in experimental animals consistently greater than 100 mg/kg (ATSDR 1992a). High barium concentrations (2 to 10 ppm) in human drinking water have been reported to be associated with elevated cardiovascular mortality, hypertension, and other cardiovascular effects (ATSDR 1992a).

Results in animal studies indicate that acute, intermediate, and chronic oral exposure to barium is not associated with any adverse hematological effects. Developmental effects reported in a study by Tarasenko et al. (1977) in rats reported effects in offspring included increased mortality, increased leukocyte count, disturbances in liver function, and increased urinary excretion of hippuric acid.

Increased blood pressure, depressed cardiac contractility and conduction, and lower cardiac ATP content were observed in rats chronically exposed to 10-100 mg Ba/L in drinking water (Perry et al. 1983 1985, 1989; Kopp et al. 1985). The NOAEL exposure level identified in these studies was 1 mg/L, or approximately 0.5 mg/kg/day.

No information on the toxicological effects of barium on avian receptors was located.

Cadmium (CAS No. 7440-43-9). Cadmium is found naturally in the environment due to chemical weathering of rocks. It is generally found in soil as free cadmium compounds (ATSDR 1993). There is no evidence that cadmium is biologically essential (Eisler 1985a). Cadmium is not reduced or methylated by microorganisms (ATSDR 1993).

Birds and mammals are comparatively resistant to cadmium toxicity as compared to aquatic species. Sublethal effects of cadmium include growth retardation, anemia, and testicular damage (Hammons et al. 1978) as cited in Eisler (1985a). Cadmium readily reacts with sulfhydral groups and may inhibit enzymatic reactions (Eisler 1985a). Bioaccumulation of cadmium has been reported in aquatic systems, however, only lower trophic levels are reported to exhibit biomagnification (Eisler 1985a). Accumulation of cadmium in avian species has been reported in liver and kidneys.

Chickens exposed to cadmium in the diet had reduced growth rates in a study by Pritzl et al. (1974). Behavioral changes were observed in young American black ducks when parents were fed 4 ppm cadmium for 4 months before egg-laying (Heinz and Haseltine 1983, as cited in Eisler 1985a).

Chromium (CAS No. 7440-47-3). Chromium (III) is an essential nutrient (for insulin function) in mammals. However, it is interconvertible in the environment with the more toxic species chromium (VI),

depending primarily on the redox potential and pH of the soil (Bartlett 1991). Chromium (VI) is generally more toxic than chromium (III). Although most chromium (VI) is reduced to chromium (III) in the acidic environment of the stomach (Donaldson and Barreras 1966), chromium (VI) compounds are absorbed significantly more efficiently from the gastrointestinal tract (2 to 10% of administered dose) than chromium (III) compounds (Outridge and Scheuhammer 1993). Once absorbed, chromium (VI) is quickly reduced to the trivalent form. The damaging effects of chromium (VI) are due to its greater membrane permeability, which allows it to cross biological membranes and oxidize cellular components not normally accessible to chromium (III). As a result, the differences in systemic toxicity are primarily attributable to differential solubilities and absorption rates of the two valence states (Franchini and Mutti 1988).

Chromium (VI) compounds are absorbed significantly more efficiently from the gastrointestinal tract (2 to 10% of administered dose) than chromium (III) compounds. Once absorbed into the blood, chromium (VI) is rapidly taken up by erythrocytes via the general anion channel, and reduced to the trivalent from by various intracellular agents (e.g., glutathione, vitamins C and E, cytochrome P450, DT-diaphorase). Uptake and subsequent reaction appear to be similar in other cell types. Despite the rapidity of these uptake processes, chromium (VI)s mobility and the limited supply of extracellular reductants causes it to be distributed more widely in the body than chromium (III). The intracellular reduction of chromium (VI) to chromium (III) generates unstable intermediate chromium (V) and chromium (IV) ions, active oxygen species (hydroxyl and superoxide radicals, singlet oxygen), and thiyl and organic radicals that are responsible for the cytotoxicity, mutagenicity, and carcinogenicity of the hexavalent form (reviewed by Manzo et al. 1992; Cohen et al. 1993; O Flaherty 1993; Outridge and Scheuhammer 1993).

As noted above, chromium exhibits a pattern of biominification rather than biomagnification in ecological food webs. Because the speciation of chromium (VI) taken up by plants is poorly understood, it is assumed to be the primary form of exposure to herbivores. However, because chromium (VI) is immediately converted to chromium (III) in animal tissues, carnivorous receptors will be primarily exposed to the less toxic trivalent form.

Pregnant female mice receiving 250 mg/L potassium dichromate in drinking water throughout gestation showed no clinical signs of toxicity, but produced significantly fewer viable offspring (Trivedi et al. 1989). In the dog, 6 mg/L in drinking water (approximately 0.3 mg/kg-day) was a chronic NOAEL [Steven et al 1976 (cited in Eisler 1986a)]. A similar level was without observable effects in a study by Anwar et al. (1961).

Rats exposed to high concentrations of chromium oxide in their diets for more than 2 years showed no decreased body weight, food consumption, life span, or histological abnormalities in major organs (Ivankovic and Presussmann 1975).

Cobalt (CAS No. 7440-48-4). Cobalt is a dietary essential for ruminants and horses in which it is incorporated into vitamin B-12. Signs of cobalt deficiency in cattle and sheep are loss of appetite, body weight loss, emanciation, and anemia. Cobalt deficiency is more likely than cobalt toxicosis.

Environmental exposures to high levels in cobalt rarely occur. Characteristic signs of chronic toxicosis for most species are species are reduced feed intake and body weight, emanciation, anemia, hyperchromemia, debility, and increased liver cobalt (Turk and Kratzer, 1960).

A study by Brewer (1940) where cobalt was mixed with the food of dogs in amounts equivalent to 5, 10, 15, and 20 and 30 mgm at no time during the course of the four week study showed any toxic signs.

Adding cobalt in the form of cobalt chloride to the diet at levels up to 200 ppm did not result in toxicosis in pigs fed a diet adequate in iron (Huck and Clawson, 1976).

A study by Hill (1979) observed growth retardation and decreased resistance to infection in chicks fed cobalt in protein mixtures.

Cobalt has a wide variety of uses including its use in superalloys (alloys that maintain their strength at high temperatures approaching their melting points) and as a catalyst. The most abundant of the radioactive isotopes of cobalt, Co-60, is produced in nuclear explosions and in reactors. Its radiological half-life is 5.27 years (Eisenbud 1987).

The transport of atmospheric cobalt depends on its state (e.g. gas, vapor, or particle) and on meteorological conditions such as wind, precipitation, topography, and vegetation. The transport of cobalt from atmosphere to soil and surface water occurs as a result of dry and wet deposition.

As for most metals, sediment and soil are the final repository for cobalt emitted into the environment by humans. Most of the cobalt released into water eventually reaches lakes via the transport river transport of dissolved and suspended particles. Cobalt is not significantly adsorbed by organic materials (e.g., humic and fulvic materials) in water.

The transport of cobalt in soil depends on its adsorption/desorption. Cobalt is retained by oxides such as iron and magnesium oxide, crystalline materials such as aluminosilicate and geothite, and natural organic substances in soil. Cobalt has a tendency to form soluble complexes with dissolved organic matter. In clay soil, the adsorption may be due to ion exchange at the cationic sites on clay with either simple ionic or hydrolized ionic species such as $CoOH^+$. At higher soil pH, the mobility of cobalt decreases, probably due to the formation of hydroxide or carbonate. The distribution coefficient of cobalt in a variety of soils ranges from 0.2 to 3800. Therefore, in most soils, cobalt is more mobile than lead, chromium, zinc, and nickel, but less mobile than cadmium (Baes and Sharp 1983; King 1988; Smith and Carson 1981).

Copper (CAS No. 7440-50-8). Copper is widely distributed in nature and is an essential element for (1) the normal function of several critical enzymes and (2) the utilization of iron. Copper deficiency is, therefore, usually a greater health concern than copper excess. Copper absorption in the gastrointestinal tract is normally regulated by body stores. Absorbed copper is transported to the liver, where it may be incorporated into ceruloplasmin (a copper transport and donor molecule) and excreted into the plasma, stored as metallothionein or in lysosomes, or excreted via the bile (reviewed by Nederbragt et al. 1984).

Depressed food intake, body-weight gain, egg number and weight, and organ weights are associated with copper excess in poultry (Stevenson and Jackson 1981). The pair-feeding study was conducted to determine whether these effects were associated with direct toxicity or the accompanying marked reduction in food intake (Stevenson and Jackson 1981). Body weight, food intake, organ weights, egg production, egg weight, clinical chemistry parameters, and organ Cu, Fe, and Zn concentrations were monitored in laying hens fed varying concentrations of copper in their diet for 6 weeks (Stevenson and Jackson 1981). A NOAEL of 24 mg/kg/day was identified and used to develop TRVs for avian functional groups.

High doses of copper have caused liver and kidney damage as well as anemia in a number of species. It has been observed that the stomach is also a target in rats and mice (Hebert et al. 1993). This well-designed subchronic feeding study examined histopathology, clinical pathology, reproductive toxicity, and tissue metal accumulation in males and females of both species.

An oral NOAEL was established in a chronic study of young calves (Cunningham 1946). The study confirms that young calves are susceptible to copper.

Lead (CAS No. 7439-92-1). Lead is a ubiquitous trace constituent in rocks, soils, plants, water, and air, with an average concentration of 16 mg/kg in the earth's crust (Eisler 1988b). Lead has four stable isotopes: Pb-204 (1.5%), Pb-206 (23.6%), Pb-207 (22.6%), and Pb-208 (52.3%). Lead occurs in four valence states: elemental (Pb^0), monovalent (Pb^+), divalent (Pb^{+2}), and tetravalent (Pb^{+4}). In nature, lead occurs mainly as Pb^{+2} and is oxidized to Pb^{+4}. Metallic lead is relatively insoluble in hard water. Some lead salts are somewhat soluble in water. Of the organoleads, tetraethyllead and tetramethyllead are the most stable and are highly soluble in many organic solvents but are fairly insoluble in water. Both undergo photochemical degradation in the atmosphere to elemental lead and free organic radicals. Organolead compounds are primarily anthropogenically-produced (Eisler 1988b).

Lead is neither essential nor beneficial to living organisms. Lead affects the kidney, blood, bone, and central nervous system. Effects of lead on the nervous system is both functional and structural. Lead toxicity varies widely with the form and dose of administered lead. In general, organolead compounds are more toxic than inorganic lead. In nature, lead occurs mainly as divalent, Pb^{2+}. Ingestion of lead shot by regulatory waterfowl is a significant cause of mortality in these species.

Hatchlings of chickens, quail, and pheasants are relatively tolerant to moderate lead exposure (Eisler 1988b). There was no effect on hatchling growth of these species at dietary levels of 500 mg/kg or on survival to 2,000 mg/kg lead (Hoffman et al. 1985 as cited in Eisler 1988b). Altricial species are generally more sensitive to lead than precocial species (Eisler 1988b) of avian insectivores. American kestrel (*Falco sparverius*) exposed to 50 mg/kg/day metallic lead in diets did not exhibit effects on survival or reproductive success (Colle et al. 1980).

Manganese (CAS No. 7439-96-5). The bioavailability of different forms of manganese varies considerably depending on different exposure conditions. There is potentially higher bioavailability of manganese from drinking water than food. It is also important to recognize that various dietary factors as well as the form of manganese can have a significant bearing on the dose absorbed from the gastrointestinal tract. For instance, many constituents of a vegetarian diet (e.g., tannins, oxalates, phytates, fiber, calcium, and phosphorus) have been found to inhibit manganese absorption presumably by forming insoluble complexes in the gut. Thus, herbivores are more likely to be resistant to manganese toxicity. Also, the form of manganese can significantly influence toxicity. For example, mice receiving the two soluble forms of manganese (chloride and acetate salts) were found to gain significantly less weight than controls, while mice consuming the insoluble forms of manganese (carbonate and dioxide salts) appeared to actually gain slightly more weight than controls.

DiPaolo (1964) subcutaneously or intraperitoneally injected DBA/1 mice with 0.1 mL of an aqueous of solution 1% manganese chloride twice weekly for 6 months. A larger percentage of the mice exposed subcutaneously (24/36; 67%) and intraperitoneally (16/39; 41%) to manganese developed lymphosarcomas compared with controls injected with water (16/66; 24%). In addition, tumors appeared earlier in the exposed groups than in the control groups. The incidence of tumors other than lymphosarcomas (i.e., mammary adenocarcinomas, leukemias, injection site tumors) did not differ significantly between the exposed groups and controls.

A study reporting the minimum manganese requirements in chickens was used to derive a TRV of 2.9 mg/kg/day. Guinea fowl were found to have reduced hatchability and increased deformed embryos when fed diets deficient in manganese (Offiong and Abed 1980).

For rats, the estimated requirement is 50 mg Mn/kg diet (Rogers 1979). A dietary reproduction study in rats exposed to 250 ppm manganese (13 mg/kg/day) was used to develop a TRV of 1.1 mg/kg/day (Laskey et al. 1982).

Mercury (CAS No. 7439-96-5). Mercury exists in the environment in three oxidation states: the elemental state (Hg^0), mercurous (Hg^{+1}) state, and mercuric (Hg^{+2}) state. Although the generally more toxic organic forms of mercury are unlikely to persist in the environment, they (in particular, methylmercury) may be formed in biotic tissues and are known to biomagnify through ecosystems, particularly aquatic systems (reviewed by Wren 1986; Scheuhammer 1987).

Because of its chemical stability and lipophilicity, methylmercury readily penetrates the blood-brain barrier. The central nervous system is thus a major target organ in both mammals and birds. However, reproductive effects have been reported at even lower doses. Methylmercury can be converted to inorganic mercury both in tissues and by microflora in the gut. The homolytic cleavage of the mercury-carbon bond leads to generation of reactive intermediates, e.g., methyl and metal radicals, which cause cellular damage (reviewed by Wren 1986; Scheuhammer 1987; Manzo et al. 1992).

The effects of mercury on avian herbivores, insectivores, and carnivores were evaluated as follows. For herbivores, the effects of organic mercury compounds on galliformes (e.g. domestic chickens, quail, and pheasants) have been investigated by several groups. However, no study was reviewed that identified a NOAEL. The lowest LOAEL for relevant endpoints (reproductive success) of several similar studies was found in a study of the effects of mercury on birds (Fimreite 1979). Reduced egg production, shell thickness, and hatchability in pheasants fed seed treated with organomercurial fungicide were observed.

Three goshawks were fed a diet of chickens that had eaten wheat dressed with an organomercurial fungicide (Borg et al. 1970). The tissue of the chickens contained 10 to 40 ppm of mercury, mostly as methylmercury. The hawks died after 30 to 47 days; their total mercury intake was about 20 mg/bird.

Two studies examined the effects of subchronic methylmercury exposure on the reproductive competence of male and female rats (Khera and Tabacova 1973; and Khera 1973). The NOAEL identified for both sexes was 0.25 mg/kg/day. Much less information is available regarding methylmercury toxicity to herbivores. In a study of acute methylmercury toxicity in mule deer (*Odocoileus hemionus hemionus*), 17.88 mg/kg was said to be the LD_{50} (Eisler 1987a). A number of studies have examined the effects of chronic methylmercury ingestion on carnivorous mammals, particularly cats (e.g., Albanus et al. 1972; Charbonneau et al. 1976; Eaton et al. 1980) and mink (e.g., Aulerich et al. 1974; Wobeser et al. 1976; Wren et al. 1987). The chronic toxicity of cats study was considered superior to other available studies because of its long duration (2 years), use of relatively large group sizes, detailed examination of endpoints, identification of both no-effect and effect levels, and administration of mercury via both contaminated fish and addition to diet (Charbonneau et al. 1976).

Nickel (CAS No. 7440-02-0). Small amounts of nickel can be essential for normal growth and reproduction (ATSDR 1988a). Oral exposure to high concentrations of nickel has been reported to adversely affect the hematological system and reproduction.

Rats fed 5 mg/kg/day nickel sulfate in a 2-year dietary study did not produce hepatic changes or altered body weights (Ambrose et al. 1976). This NOAEL was supported by a rat subchronic drinking water study conducted by American Biogenics Corp. (1986) and a rat reproductive study by Research Triangle Institute (RTI 1987). For mammalian herbivores, a subchronic study of cows that did not exhibit reduced food intake or growth rate when fed 250 mg/kg/d nickel carbonate (O'Dell et al. 1979 as cited in NAS 1980). A dietary study exposing dogs to 1,000 ppm nickel did not result in adverse effects (Ambrose et al. 1976).

In a three-generation study by Ambrose et al. (1976), no adverse effects on fertility, gestation, viability and lactation were noted in rats maintained on diets containing nickel sulfate hexahydrate at 0, 250, 500, or 1,000 ppm nickel.

A study by Eastin and O'Shea (1981) fed mallard ducks nickel at concentrations of: 0, 12.5, 50, 200, or 800 ppm. The ingestion had no effect on egg production, hatchability, or survival of ducklings.

Nitrate. *Homo sapiens* have been identified as the most sensitive species. Several studies (Bosch et al. 1950; Walton 1951; Sattelmacher 1962; Simon et al. 1964) indicate that infants' ingestion of formulas made with nitrate-contaminated groundwater at concentrations greater than 10 mg/L caused cyanosis. In infants, the pH of the gastrointestinal system is higher than in adults and this allows for the growth of nitrate-reducing bacteria. These bacteria convert nitrate to nitrite, which then causes methemoglobinemia. Therefore, for humans, the NOAEL is 1.6 mg nitrate as nitrogen/kg-day. Nitrates are a normal component of the human and animal diet.

However, in animal studies, the NOAELs and LOAELs identified are typically much higher. In animal studies, Hugot et al. (1980) identified a LOAEL of 900 mg nitrates as nitrogen/kg-day. This LOAEL is based on a three generation study of rats at doses of 90 to 160 mg nitrate as nitrogen/kg-day administered as sodium nitrate. There were no effects on the reproductive capabilities, but small decreases in birth weight, growth rate during lactation, and changes in organ weights at weaning were observed. A LOAEL of 90 mg nitrates as nitrogen was identified, and assuming that 10% of the nitrate is converted to nitrite, a LOAEL of 900 mg nitrates as nitrogen/kg-day.

Reproductive NOAELs have been observed for hamsters and mice at 66 mg/kg-day (FDA 1972a,b) when administered on days 6-10 and 6-15 of gestation, respectively. Another reproductive NOAEL was determined by Sleight and Atallah (1968) for guinea pigs at 143-204 days. Four dose levels were administered at 12, 102, 507, and 1130 mg nitrates as nitrogen/kg-day. Nitrate at the highest dose level reduced the number of live births, but no adverse effects were observed at the other dose levels.

In drinking water, Druckrey et al. (1963) supplied rats with 20 mg nitrates as nitrogen/kg-day for three generations. No teratogenic effects or adverse effects on reproduction were detected in any generation. Assuming that 10% of the nitrate is converted to nitrite, a NOAEL of 200 mg nitrates as nitrogen/kg-day was established.

Selenium (CAS No. 7782-49-2). Selenium is a critical nutrient and a key component of several enzymes (Eisler 1985b). It is often found in high concentrations in areas where soils have been derived from Cretaceous rocks (Eisler 1985b). Selenium does accumulate to high concentrations in certain species of plants (e.g., *Aster, Astragalus*) (Eisler 1985b). Livestock species ingesting these plants have been reported to exhibit toxic symptoms such as abnormal movements, labored breathing, dilated pupils, bloating, diarrhea, and rapid pulse. No effective treatment is known for counteracting the toxic effects of high levels of ingested selenium. Prolonged exposure to more moderate levels of selenium result in skin lesions involving alopecia, hoof necrosis and loss, emaciation and increased serum transaminases, and alkaline phosphatase in animals (TOXNET 1994). Selenium has been reported to cause growth retardation, decreased fertility, embryotoxicity, fetotoxicity, and teratogenic effects in animals (TOXNET 1994). Birds appear to be particularly susceptible to selenium, particularly in the area of reproductive success. Malformations in chickens and waterfowl have been widely reported (EPA 1993a).

Selenium deficiency is often a greater threat to health than selenium poisoning (Eisler 1985b). Selenium deficiency has been documented in a variety of species including fish, quail, ducks, poultry, rats dogs, domestic grazing animals, antelope, monkeys, and humans (Eisler 1985b). Selenium can also reduce the toxicity of other heavy metals such as thallium, arsenic, and copper (Wilber 1980).

In a study by Rosenfeld and Beath (1954), selenium administered as potassium selenate to sires and pregnant rats through five breeding cycles did not affect reproduction, the number of young reared, or on the reproduction of two successive generations of dams and sires in groups receiving 1.5 ppm selenium. Selenium doses as low as 3.2 mg/kg body weight have resulted in death in sheep (Eisler 1985b).

Silver (CAS No. 7440-22-4). The precious metal silver is relatively rare in the earth's crust and does not occur regularly in animal tissues. As a result, the toxicity of silver has been little studied. Approximately 1-10% of ingested silver is absorbed; as much as 18% may be retained. Silver-protein complexes accumulate in the liver, and biliary excretion (complexed with glutathione) is the major route of elimination. In most tissues, silver is deposited as large granules. With rare exceptions, these deposits are not associated with adverse effects. The LD_{50} of silver in rats is relatively high at 24 mg/kg (reviewed by Rungby 1990).

Silver causes a conditioned deficiency of selenium in rats, decreasing tissue levels of selenium, and the selenoprotein glutathione peroxidase (Ganther 1980). Silver ions complex strongly to sulfhydryl groups and cause preoccupation of hepatocellular membrane lipids (Rungby et al. 1987; Shinogi and Maeizumi 1993). Because of its affinity for sulfhydryls, the degree of binding to cellular macromolecules and toxicity of silver is mitigated by induction of the divalent metal-binding protein metallothionein (Shinogi and Maeizumi 1993). Exposure of fetal and adult rats to silver resulted in deposition in the central nervous system (CSN) (Rungby and Danscher 1983a, b). Pyramidal cells in the developing hippocampus appears to be a sensitive target, exhibiting reduced cellular volume in both pre- and postnatally exposed rats (Rungby et al. 1987; Rungby 1990).

A study by Rungby and Danscher (1984) in which mice exposed to approximately 18 mg/kg day were observed to be "hypoactive." Although silver deposits occurred in certain motor centers of the brain, no association between the concentration of deposits and the extent of hypoactivity was found.

No information on the toxicological effects of silver on avian receptors was located.

Sulfate (CAS No. 14808-79-8). Sulfates are generally of low toxicity. Several studies indicate no adverse effects when sulfate compounds are administered (Brown and Gamatero 1970; Sasse and Baker 1974; Paterson et al. 1979) and others that list the effects of loose feces and decreased intake (Bird 1972; L'Estrange et al. 1969). These five studies were conducted using pigs, chicken, and sheep. One study listed an LD_{50} for a single-dose injection of sodium sulfate monohydrate in mice of 45.6 mg/kg day (Nofre et al. 1963).

No other information was found for the toxicity of sulfate.

Thallium (CAS No. 7440-28-0). Thallium is a nonvolatile heavy metal element that is not used extensively by industry, but is mainly introduced into the environment as a waste product of other metals. Thallium can exist in the atmosphere as an oxide, a hydrazide, a sulfate, or a sulfide. Thallium is present in mono- or trivalent forms in the environment. Thallium(III) forms some organometallic compounds and thallium (I) forms relatively few complexes with the exception of those with halogen, oxygen, and sulfur ligands. Thallium can be removed from solution by adsorption onto clay minerals, bioaccumulation, or (in reducing environments) precipitation of the sulfide. Increased pH values have been found to produce extensive thallium-humic acid interactions while lowering thallium-inorganic interactions. Thallium may be bioconcentrated by living organisms (Callahan et al. 1979). Thallium(I) is more stable and resembles the alkali metal cations in many of its chemical properties. Thallium(III) forms many organic compounds (Zitko 1975), the toxicity of which has been little explored.

Thallium is slightly more acutely toxic to mammals than mercury. The similarity between kinetic profiles of inorganic trivalent and monovalent thallium species suggests that they are converted in vivo to one chemical form, probably monovalent thallium (Sabbioni et al. 1980). Isomorphic with potassium, thallium (I) is readily absorbed and distributed throughout the body, and can substitute for potassium and other monovalent cations in enzymatic reactions. The affinity of thallium (I) for enzymes is 10 times higher than that of potassium, which may cause the observed toxic effects (Zitko 1975). Thallium (I) uncouples oxidative phosphorylation, adversely affects protein synthesis, and inhibits a number of enzymes including alkaline phosphatase and succinic dehydrogenase (Zitko 1975). Thallium is also toxic to plants, inhibiting chlorophyll formation and seed germination.

A study in the 1930s of the acute toxicity of thallium sulfate in game birds including quail (Shaw 1933) formed the basis for the TRV for these functional groups. In a study of the acute toxicity of thallium sulfate in three immature golden eagles (Aquila chrysaetos), the acute oral LD_{50} was estimated to be between 60 and 120 mg/kg (Bean and Hudson 1976). Using the lower end of this range as the QCE, a TRV for raptorial birds at the INEL was derived.

Rats exposed to thallium in their drinking water have shown effects on various neurological (Manzo et al. 1983. Rossi et al. 1988) and reproductive (Formigli et al. 1986) endpoints. Because of the clear ecological relevance of reproductive impairment, a QCE was selected from the study of thallium-induced testicular toxicity (Formigli et al. 1986).

Vanadium (CAS No. 7440-62-2). Vanadium occurs naturally in igneous rock, and shales, in some uranium and iron ores and in association with fossil fuels. In the environment, vanadium is usually combined with oxygen, sodium, sulfur, or chloride (ATSDR 1990). There is no indication that vanadium is nutritionally required by higher plants and annuals (Ammerman et al. 1973). Vanadium uptake into above ground parts of terrestrial plants is low. However, some legumes have been identified as vanadium accumulators (ATSDR 1992). In general, bioconcentration and biomagnification in terrestrial environments appears limited.

Most toxic effects of vanadium are associated with inhalation of vanadium pentoxide (ATSDR 1992). Vanadium is poorly absorbed in the gastrointestinal tract and most is excreted unabsorbed in feces (ATSDR 1992). Ingestion of high levels of vanadium are reported to cause dehydration, emaciation, and diarrhea (Ammerman et al. 1973).

A study of vanadium toxicity in female leghorn chickens by (Kubena and Phillips 1982) was used to develop a TRV of 0.85 mg/kg/kay. A TRV of 0.25 mg/kg/day was derived using a study of the effects of vanadium to mallards (White and Dieter 1978).

A study of the effects of vanadium to mice (Schroeder and Balassa 1967) was used to derive a TRV of 0.5 mg/kg-day for vanadium. There is little information in the literature regarding vanadium toxicity in reminants (Ammerman et al. 1973). A study was used to derive a TRV of 0.42 mg/kg/day (Abbey 1968).

The majority of vanadium is used as an alloying agent (Hillard 1987). Vanadium compounds also have an important role as industrial catalysts. Vanadium-containing catalysts are used in several oxidation reactions such as the manufacture of phthalic anhydride and sulfuric acid. There are also used as corrosion inhibitors in flue-gas scrubbers.

From man-made sources almost all the vanadium released to the atmosphere is in the form of simple or complex vanadium oxides (Byerrum et al. 1974). Vanadium transported within the atmosphere is eventually transferred to soil and water on the earth's surface by wet and dry deposition (Duce and Hoffman 1976).

The transport and partitioning of vanadium in water and soil is influenced by pH, redox potential, and the presence of particulate. It has a natural concentration in groundwater ranging from less than 1 to 10 ppb (Dragun 1988). In water, vanadium generally exists in solution as the vanadyl ion (V^{+4}) under reducing conditions and the vanadate ion (V^{+5}) under oxidizing conditions, or as an integral part of, or adsorbed onto, particulate matter (Wehrli and Stumm 1989). The partitioning of vanadium between water and sediment is strongly influenced by the presence of particulate in the water. Vanadium is transported in water in one of two ways: solution or suspension. It has been estimated that only 13% is transported in solution, while the remaining 87% is in suspension (WHO 1988). Vanadium has a typical native soil concentration range of 20 to 500 parts per billion (ppb).

The mobility of vanadium in soils is affected by the pH of the soil. Relative to other metals, vanadium is fairly mobile in neutral or alkaline soils, but its mobility decreases in acidic soils (Van Zinderen Bakker and Jaworski 1980). Similarly, under oxidizing, unsaturated conditions some mobility is observed, but under reducing, saturated conditions vanadium is immobile (Van Zinderen Bakker and Jaworski 1980).

Zinc (CAS No. 7440-66-6). Zinc is found naturally in the environment and is present in all foods (ATSDR 1988b). It is an essential element and occurs in the environment in the 2+ state. Zinc is likely to be strongly sorbed to soil. Relatively little land disposed zinc is expected to be in a soluble form. Bioconcentration factors of soil zinc by terrestrial plants, invertebrates, and mammals are 0.4, 8, and 6, respectively (ATSDR 1988b).

Excessive dietary zinc has been shown to cause copper deficiency and anemia (ATSDR 1988b). Cadmium has also resulted in the redistribution of zinc to the liver and kidney. Health effects associated with zinc exposure include anemia, liver necrosis, fetal resorption, and in extreme cases, cessation of reproduction (ATSDR 1988b).

A study of sheep by Allen et al. (1983) revealed pathological changes in liver and kidney.

7.3.5 Development of TRVs for Organic Contaminants of Potential Concern

This section contains summaries of the information used to determine the TRVs for the organic contaminants for which toxicological studies were located. The organic contaminants include:

- 2-methylnaphthalene
- acetone
- Aroclor-1254 (PCBs)
- PAHs
- TPH
- xylene

Toxicity information was not found for the following organic contaminants:

- 4-methyl-2-pentanone
- chloromethane
- dibenzofuran
- pentachlorophenol

Toxicity properties for benzo(a)anthracene, benzo(a)pyrene, benzo(b)fluoranthene, benzo(g,h,i)perylene, benzo(k)fluoranthene, chrysene, dibenz(a,h)anthracene, indeno(1,2,3-cd)pyrene, 2-methylnaphthalene, and pyrene are discussed in the polycyclic aromatic hydrocarbons (PAHs) summary. No specific summary for Aroclor-1254 was located so a general summary about PCBs was used.

The development of TRVs for the studies identified for each COPC is contained in Appendix I.

Acetone (CAS NO. 67-64-1). Acetone is a common air contaminant that is moderately toxic by various routes. It is a skin and eye irritant and is narcotic in high concentration (Sax and Lewis 1987).

Acetone was administered via gavage for 90 days to a group of albino rats (30 each sex per treatment group) at treatment levels of 0, 100, 500, or 2500 mg/kg-day (EPA 1986b). Body weights, clinical chemistry, hematology, histopathologic parameters, food consumption, and organ weights were measured. No effects were observed at the 100 mg/kg-day dose. Histopathologic studies showed that rats in the 2500 mg/kg-day group had a marked increase in tubular degeneration of the kidneys and hyaline droplet accumulation with increasing dose.

Inhalation exposure to acetone for a few hours has resulted in rats at concentrations ranging from 16,000 to 50,600 ppm (Bruckner and Peterson 1981) and in guinea pigs from 10,000 to 50,000 ppm (Specht et al. 1939).

No reproductive effects (i.e., no effects on the number of implants/litter, percent live pups/litter, or mean percent resorptions/litter were observed in rats or mice in an inhalation developmental study (NTP 1988). No effects were observed on the fertility of male Wistar rats treated with drinking water containing acetone at 1,071 mg/kg/day for 6 weeks (Larsen et al. 1991).

No information on the toxicological effects of acetone avian receptors was located.

PAHs. In general, unsubstituted PAHs do not tend to accumulate in mammalian adipose tissues despite their high lipid solubility (Eisler 1987b). This is probably because PAHs are rapidly and extensively metabolized. Numerous PAHs are distinct in their ability to produce tumors in most mammal species tested. Acute and chronic exposure to various carcinogenic PAHs has resulted in destruction of the hematopoietic and lymphoid tissues, ototoxicity, respiratory epithelia, and other effects (Eisler 1987b). For the most part, tissue damage occurs at dose levels expected to cause cancer; therefore, the threat of malignancy is the predominant health effect of concern. Target organs affected by PAHs are diverse, probably because of the widespread distribution of PAHs in the body and selective attack by PAHs on proliferating cells. Laboratory studies with mice show that many PAHs affect animals' immune systems. Although ecotoxicological data are scarce, the tendency is for many PAHs to be either carcinogenic (high molecular weight compounds) or acutely toxic (low molecular weight compounds) to many organisms. In addition, chronic toxicities, mainly seen as increased frequencies of hyperplasia and neoplasia in

aquatic invertebrates, fish, and amphibians, have been demonstrated in areas with high sediment PAH concentration (Eisler 1987b).

Studies done on mallards revealed no signs of mortality or toxicity during exposure in the adults but produced significant reduction in embryonic growth and a significant increase in the percent of abnormalities, e.g., incomplete skeletal ossification, defects in the eye, brain, liver, feathers, and bill (Hoffman and Gay 1981).

PCBs (CAS 1336-36-3) (Aroclor-1254). PCBs comprise a physicochemically and toxicologically diverse group of 209 compounds whose widespread use and chemical stability have made them ubiquitous in the environment. Because of their generally low acute toxicity, effects on environmental receptors are more likely to be sublethal and chronic than acute. Toxicity and risk assessment of PCB mixtures is complicated by the fact that the 209 congeners differ markedly in both the severity and the nature of their biological effects. The toxic potency of individual congeners is dependent upon their structure. While the approximate isostereomers of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD)—i.e., coplanar molecules with chlorine atoms in the lateral (but not ortho) ring positions—are the most toxic (and carcinogenic in some species), many others manifest very low acute or chronic toxicity.

The most toxic congeners are also the most potent inducers of mixed-function oxidases as well as some Phase II enzyme activities (reviewed by Safe 1992). These enzymes metabolize not only the inducing PCBs but also a variety of endogenous molecules, such as steroid hormones, that are necessary for normal physiological function. As a result, PCBs may exert adverse effects on development and reproduction in various vertebrate species, including birds (e.g., Koval et al. 1987). In addition, there is considerable difference in the sensitivity of various species to these compounds. Particularly sensitive species include some birds, guinea pigs, and mink (McConnell 1985).

Dahlgren and Linder (1971) and Dahlgren et al. (1972) examined the effects of Aroclor-1254 exposure in pheasants. Although no NOAEL was identified in this work, its focus on a wild species and dosing of both sexes makes it attractive for TRV development. Nine to 10 mg/kg-day Aroclor-1254 reduced sperm concentrations in American kestrels, *Falco sparverius* (Bird et al. 1983).

Linder et al. (1974) identified NOAELs for Aroclor-1254 in a two-generation reproductive study in rats. Many studies have focused on the toxicity of various PCBs to mink, which is a sensitive species (Eisler 1986b; EPA 1993b). Related species such as otter and ferret are considerably less susceptible, suggesting that extrapolation from mink to receptors at the INEEL may not be appropriate.

Total Petroleum Hydrocarbons (TPHs). Petroleum is a combination of several products in varying amounts and combinations. Petroleum is composed of but is not limited to: Gasoline, Diesel, Fuel Oil No.2, Fuel Oil No.4, Kerosene, JP-4, JP-5, and Used Oil. Each of these products is a complex mixture of several hundred hydrocarbon compounds (PAHs, benzene, toluene, ethylbenzene, xylenes, ethylene dibromide, 1,2-dichloroethane, and methyl tert-butyl ether) and other additives (e.g., anti-knock agents, corrosion inhibitors, anti-oxidants, etc.). The actual composition of these products varies depending on the source, age, temperature, and other factors and conditions. Thus, no unique composition exists for any of the aforementioned products. The behavior of these products in the environment depends on the properties of the individual constituents and their concentrations (State of Idaho 1996).

Although no toxicological data are available for TPHs per se, data were obtained for JP-4, a jet fuel petroleum product. No studies on the teratogenicity, embryotoxicity, or reproductive effects are available. Although no LD_{50} was found for JP-4, and oral LD_{50} of 20 g/kg has been reported for kerosene in guinea pigs. Chronic inhalation studies have been conducted with JP-4 in rats, mice, and dogs. No other information was found for the toxicity of TPHs.

The TRVs for benzene was used for TPHs and is thought to have similar toxicity and fate and transport properties.

Xylene (CAS No. 1330-20-7). Acute exposure to xylene via inhalation primarily caused central nervous system (CSN) effects, although acute liver injury was observed in guinea pigs given 1 to 2 g/kg-day intraperitoneally (WHO 1981). An oral LD_{50} value of 4300 mg/kg has been reported for rats (1984, TOXNET). Chronic studies indicate that xylene has a relatively low toxicity over the long-term. No changes were found in rats, guinea pigs, dogs, and monkeys continuously exposed to 80 ppm for 127 days nor in rats exposed to 700 ppm for 130 days (WHO 1981). Ungvary et al. (1980) evaluated the toxicity of xylene in rats. Rats were exposed via inhalation to 35, 300, or 700 ppm continuously on days 7 through 14 of gestation. No adverse effects were observed, and the authors concluded that xylene was not teratogenic. A commercial mixture of xylene was given to mice via gavage at doses of 0, 520, 1030, 2060, 2580, 3100, or 4130 mg/kg-day on days 6 through 15 of gestation (Marks et al. 1982). No adverse effects were observed in either dams or fetuses exposed to levels of 1030 mg/kg-day or less. An exposure of 2060 mg/kg-day and higher approached lethal levels in dams. Fetal weight was significantly decreased and the average percentage of malformations in fetuses significantly increased at these dose levels.

A NOAEL of 250 mg/kg-day was developed based on a well-designed study with animals from two species—F3444N/N Rats and B6CF1 Mice. Adult males and females were tested for 103 weeks and a comprehensive histology was performed.

No data on the toxicological effects of xylene to avian receptors were available.

7.3.6 Identifying Uncertainty Associated with TRVs

The following paragraphs identify the uncertainty associated with the TRVs.

Although QCEs should be derived from the best available literature and all the uncertainties that could be reasonably accounted for are included in the AFs used to calculate TRVs, it is unlikely that any single scheme could suffice to extrapolate available toxicity data for all chemicals among all species. Thus, the remaining uncertainty in these criteria may be even greater than that associated with exposure estimation. Some of the extrapolations required in TRV development are listed in Table 7-18. TRVs are themselves dependent not only on extrapolation procedures but also on sampling adequacy and analytic accuracy, and the completeness and accuracy of response measurements in variable populations of test organisms. Combining results from different species, gathered under different experimental conditions, and extrapolation of results in test organisms to populations of resident species introduce additional, potentially significant sources of error. These errors are:

- While classical human toxicology relies on extrapolation of toxicity data from a handful of mammalian species to one species, an ecotoxicological evaluation must rely on extrapolation from a few test species to a larger number of receptor species spanning variable (and often large) ranges in terms of phylogeny, anatomy, physiology, and life histories. Further, the spatial and temporal heterogeneity of exposure and conditions in natural systems can cause large variations in the doses and responses observed.

- Organisms in the environment are rarely (if ever) exposed to pure compounds alone, but rather to complex mixtures of chemicals whose synergestic effects are unknown.

- Chemicals may be volatilized and transformed to more or less toxic products sequestered in the environment.